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A Hypereosinophilic Syndrome Associated with HIV Infection

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ABSTRACT

A hypereosinophilic syndrome associated with dermatitis has been observed rarely in association with HIV infection. We report the case of a young man with AIDS who presented with a diffuse cutaneous eruption, fever, angioedema, eosinophilia and a mildly elevated serum IgE. No allergic or infectious cause of this illness could be determined and the patient was treated with corticosteroids and PUVA therapy with complete resolution of the dermatitis and associated findings. The case exhibited clinical and histopathologic similarities to the idiopathic hypereosinophilic syndrome as well as acute graft-versus-host disease. A serum determination of the cytokine, IL-5, which is associated with eosinophil production, was found to be mildly elevated during the peak of the eruption while samples drawn previously and subsequently were not. A brief review of the literature concerning eosinophils and HIV infection is presented in the context of the present case.

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INTRODUCTION

Eosinophils function as effective killers of helminths and other multicellular organisms (1). Increased production of eosinophils has been observed not only in parasitic infections but also in atopia, drug reactions, neoplasms or may occur idiopathically (2,3). T-cells and monocytes play prominant roles in modulating the defensive eosinophilic response by controlling the generation, migration and function of eosinophils (3). Abnormalities of T-cell or monocyte function such as those associated with HIV infection would be anticipated to result in aberrant eosinophilic responses.

It has been recently observed that eosinophilia and abnormal production of eosinophil products occur in many patients with advanced HIV infection (4,5). May and colleagues reported two cases of a predominantly cutaneous hypereosinophilic syndrome in HIV-infected patients with advanced disease (6). We present an additional case of this entity in whom IL-5, a cytokine which regulates eosinophil production, was found to be elevated during the eruption but was not in prior or subsequent samplings.

CASE REPORT

A 29 year old white male with AIDS presented in May 1991 with worsening of an intensely pruritic skin rash which had been developing since mid-March. The eruption covered his face, trunk,

back and extremities. The eruption on the face had resulted in severe swelling and he had been experiencing fevers, chills and severe malaise over the three days prior to admission. The patient had been found to be HIV-seropositive in 1987 and suffered a continued loss of CD4 cells, becoming anergic and developing thrush by 1989. He also exhibited recurrent anorectal Herpes Simplex type II infection, defining him as having AIDS in May 1990. He had received zidovudine for approximately 6 months but had discontinued therapy in August of 1990 for persistent nausea. He declined any further anti-retroviral therapy. Prior to the development of the rash, the patient had been feeling quite well and his only medications were pentamidine 300 mg aerosolized q month, acyclovir 200 mg po tid and ketoconazole 200 mg po qday. He had been receiving all of these medications for over a year. He had no history of atopy or prior drug allergies.

The physical examination on presentation revealed an ill-appearing but well-nourished white male with a temperature of 38 degrees C. The patient had an intensely erythematous eruption involving the extremities, trunk, back and face (Figs 1, 2). The eruption consisted of erythematous macules and periadnexal papules coalescing to form scaly plaques. The eruption seemed to originate from adnexal structures with prominant palm and sole involvement. The face was markedly swollen but was non-tender. The oral cavity had a generalized erythema with erosions of the mucosa noted on the hard palate. The remainder of the physical examination was unremarkable. Admission laboratories revealed a WBC of 8100/ cu mm

with 42% eosinophils. Of note, an increasing number of eosinophils had been noticed since January of that year. The HCT was 38.1% and an erythrocyte sedimentation rate was 33 mm/hr. CD4-cell count was 24 cells/cu mm. Serum IgE was 353 IU/ml (Normal range: 0 to 180).

A bone marrow biopsy was performed which revealed a 12% mature eosinophilic infiltrate and overall hypercellularity. Routine, mycobacterial and lysis-centrifugation cultures of blood and marrow were negative. Skin biopsies at the peak of the eruption demonstrated psoriasiform hyperplasia of the epidermis with focal interphase change with apoptotic/necrotic keratinocytes and exocytosis of eosinophils as well as mononuclear cells into the epidermis. Within the dermis there was a perivascular lymphohistiocytic infiltrate containing both plasma cells and eosinophils (Fig 3). Special stains and cultures of the skin biopsy were negative. Stool analysis for ova and parasites was negative on several occasions. The hypothesis that the rash represented a severe drug-induced eruption was entertained but felt unlikely because of the nature of the drugs and the duration with which they had been received previously in addition to the characteristics of the rash.

The patient was begun on prednisone 40 mg bid and within 2 days had defervesced and experienced resolution of the eosinophilia and the facial swelling. He was also begun on oral photochemotherapy (PUVA) at a starting dose of 0.5 J/cm2 and 20 mg of methoxsalen. Therapy was administered twice weekly and increased by 0.5 J/cm2 per treatment. The prednisone was weaned in

conjunction with the PUVA. After receiving a cumulative dose of 52.5 J/cm2 (14 treatments) the patient had experienced near-total resolution of the eruption and was left with residual postinflammatory hyperpigmentation in previously affected areas (Fig 4). The prednisone was tapered to a maintenance dose of 5 mg per day. He was maintained on weekly PUVA (5 J/cm2) for 13 additional treatments after which therapy was discontinued. The IgE had decreased to 252 IU/ml (Normal 1 to 180) by 4 months and would normalize by a year. In February 1992, after 2 months without PUVA, the patient began to develop the beginnings of a relapse of the eruption associated with eosinophilia. He was quickly treated with steroids and PUVA with rapid resolution and has remained on PUVA maintenance and low dose prednisone with no further relapses to date. His general health remains fairly stable as of this report (November 1992).

Aliquots of sera samples held at -70 degrees C obtained before, during and after the patient's eruption were tested with controls using specific immunoenzymatic assays in duplicate for IL-5 and IL-4 as previously described (7,8). The limits for detectability in the assays are 25 pg/mcl for IL-4 and 10 pg/mcl for IL-5. The specificity of these assays and their performance characteristics have been described previously (9,10). Results in are presented in Table 1.

DISCUSSION

The syndrome of skin eruption and eosinophilia associated with HIV infection as described in this case report is somewhat reminiscent of the idiopathic hypereosinophilic syndrome (11). In addition to the rash, the patient also demonstrated angioedema and mouth ulcerations, both of which have been observed previously in the hypereosinophilic syndrome or its variants (12,13). He did not, however, exhibit the very high degree of eosinophilia nor did he have clinical evidence of parenchymal visceral infiltration which is more characteristic of the idiopathic hypereosinophilic syndrome. The cutaneous features, degree of eosinophilia and response to treatment of the cases associated with HIV infection described by May et al, however, were very similar to that of ours and suggests a relationship (6).

Eosinophilic folliculitis is a papular eruption which occurs in HIV patients with moderate to advanced HIV infection (14). The dermatopathology of eosinophilic folliculitis is primarily characterized by follicular abscess formation involving a neutrophilic and eosinophilic inlammatory infiltrate. These findings were not observed in the case presented herein.

This patient's eruption appeared to arise in a periadnexal distribution. Initially the eruption appeared papular and later coalesced to a diffuse form. This clinical progression of the eruption is characteristic of graft-versus-host disease (GVHD), and has been used in transplant patients to differentiate eruptions due

to GVHD from drug eruptions which lack this feature (15). The involvement of palms and soles can also be observed in GVHD (16). Indeed the overall cutaneous features including the spectrum of histopathologic features are quite consistent with those observed in GVHD (17,18). This patient, however, did not exhibit any of the systemic features of more severe acute GVHD such as diarrhea, hepatosplenomegaly, pulmonary infiltrates or central nervous system irritability. Likewise, this patient had never received any blood product during his lifetime to account for an acquired GVHD. GVHD is known to be a syndrome of disordered immune regulation with features of both immunodeficiency and autoimmunity (19). Of interest, GVHD is also associated with eosinophilia (20). We postulate that the syndrome described by the current case was also due to immune dysregulation, in this case induced by HIV infection rather than the infusion of immunocompetent non-syngeneic cells. Changes consistent with immunostimulatory GVHD have been associated with other acute and reactivated viral infections including HIV-1 (21,22). In addition, in a large study of inflammatory dermatoses in which an infectious etiology was eliminated, an increasing spectrum of changes consistent with GVHD was observed with HIV disease progression (23). This case and those of May and colleagues may represent extremes of this pathophysiology.

Cytokines produced by mononuclear cells are involved in regulating the production and functioning of mature eosinophils (24). Eosinophil differentiation is induced by the cytokine, IL-5 (25). The patient described in this report had a documented

elevation in IL-5, albeit a mild one, associated with the peak of his illness which resolved on therapy. Abnormal production of other cytokines such as gamma interferon and IL-6 (26,27) has been described previously in HIV-infected individuals. It is tempting to speculate that the HIV-associated hypereosinophilic syndrome described herein is due to a dysregulated overproduction of IL-5. It is important to note, however, that eosinophils, themselves, can produce IL-5 (28) and the mild increase detected may have been a result rather than a cause of the eosinophilia. The fact that the patient had an undetectable IL-5 level in March despite a rising degree of eosinophilia since January suggests otherwise, however. Increased levels of IL-5 have also been observed in the sera of patients with diverse etiologies of their eosinophilia including the idiopathic hypereosinophilic syndrome, parasitic infections and the tryptophan-induced eosinophilia-myalgia syndrome (7,29,30,31). It has been recently observed that patients with advanced HIV infection frequently have abnormal elevations of serum eosinophil cationic protein (4), a substance released from eosinophils in response to IL-5 (32). This suggests that IL-5 activity may be generally increased in advanced HIV infection and our patient may represent a pathologic extreme. This conjecture merits further investigation.

It has been determined that eosinophils express CD4 on their surfaces and hence can bind to gp120 of HIV (33). Also bone marrow-derived eosinophils can support HIV replication (34). This further complicates the already complex relationship between HIV, cytokines

and eosinophils. Indeed, a recent large prospective study by Smith et al suggests that a degree of eosinophilia may be advantageous for survival in advanced HIV infection (5).

T-cell clones can concomitantly produce both IL-5 and IL-4 (35). IL-4 is the cytokine responsible for regulation of IgE (36). This patient had a slightly elevated IgE but measurement of serum IL-4 was negative in the immunoassay. Elevations of serum IgE in the range of this patient have been previously reported in both atopic and non-atopic HIV-infected individuals (37). A recent study demonstrated that the rise of the serum IgE is directly correlated to the decrease in CD4-cells (38). As the clinical correlate of elevated IgE levels, a higher incidence of atopic manifestations have been observed in HIV-infected individuals (39).

May and colleagues noted a beneficial response to corticosteroids and PUVA in their patients as in ours (6). Notably, corticosteroids have been utilized in the treatment of both idiopathic hypereosinophilic syndrome and GVHD (3,40). PUVA has also been employed successfully in the treatment of the idiopathic hypereosinophilic syndrome (41). PUVA therapy has been shown to be well-tolerated in HIV-infected patients (42). Interferon has also been used successfully to treat the idiopathic hypereosinophilic syndrome and may be useful in HIV-associated cases in lieu of the already low levels of interferon-gamma in HIV patients and its negative effect on IL-5 production (43).

In summary, we have presented the case of a young man with AIDS who developed an intensely pruritic, erythematous skin

eruption associated with hypereosinophilia which responded to corticosteroids and PUVA therapy. This syndrome was associated with a measurably elevated serum IL-5, a cytokine which regulates eosinophil production, although a cause and effect relationship between IL-5 and this entity will require further investigation.

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FIGURES

1. B/W photograph - Patient's face. Note severe swelling, erythema and scaling

2. B/W photograph - Patient's trunk. Note confluence of the eruption.

3. Color Photomicrograph of skin biopsy of the eruption in May at its peak with a close-up of a rete pegs showing interphase changes with apoptotic/necrotic keratinocytes and exocytosis of eosinophils as well as mononuclear cells into the epidermis. Within the dermis there is a lymphohistiocytic infiltrate containing plasma cells and

eosinophils. Epidermis is at the top, right of the figure. (hematoxylin and eosin, 300X).

4. B/W photograph - Patient's face after two weeks of therapy. Note resolution of the swelling and eruption with residual post-inflammatory hyperpigmentation and scant scaling.

TABLE 1

DATE	IL-4 (pg/ul)	IL-5 (pg/ul)	EOSINOPHILS (cells/ cu mm)
January 1991	NA	NA	1600
March 1991	< 25	< 10	NA
May 1991	< 25	16	3402
October 1991*	< 25	< 10	320
Normal control	< 25	< 10	67

NA - data not available
* - values obtained while on therapy